A first-in-human phase 1 study of LOXO-435, a potent, highly isoform-selective FGFR3 inhibitor in advanced solid tumors with FGFR3 alterations (Trial in Progress)

Gopa Iyer1, Arlene Siefker-Radtke2, Matthew Millowisky3, Neal Shore4, Xin Gao5, Melissa Reimers6, Noah Hahn7, Rasha Cosman8, Nobuaki Matsubara9, Andrea Necchi10, Debbie Robbrecht11, Armelle Vinceneux12, Enrique Grande13, Jae-Lyun Lee14, Tian Zhang15, Tornd Muren16, Ulrich M. Lauer17

1Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; 2Department of Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 3Department of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; 4Department of Internal Medicine, Washington University in St Louis, St Louis, MO, USA; 5Department of Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; 6Department of Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; 7Department of Surgery, Boston University School of Medicine, Boston, MA, USA; 8Department of Medicine, Division of Hematology/Oncology, University of California, Irvine, CA, USA; 9Medical Oncology, Earle A. Chiles Cancer Center, Seattle, WA, USA; 10Department of Hematology/Oncology, M.D. Anderson Cancer Center, Houston, TX, USA; 11Department of Hematology and Oncology, AstraZeneca, London, UK; 12Department of Genitourinary Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy; 13Department of Urology, Woman's Hospital Center; 14Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 15National Cancer Center Hospital East, Chiba, Japan; 16Department of Urology, University Medical Center, Utrecht, the Netherlands; 17Department of Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

Background

• Alterations in the fibroblast growth factor receptor 3 (FGFR3) have been identified as oncogenic drivers in solid tumor malignancies, including urothelial carcinoma1
• Available pan-FGFR inhibitors target all 4 isoforms of FGFR (FGFR1-4) and consequently their efficacy can be limited by off-target toxicity including gastrointestinal, oral mucositis, and cutaneous/nail, as well as FGFR1-mediated hyperphosphatemia2
• LOXO-435 is a potent, highly isoform-selective FGFR3 inhibitor that is designed to preserve activity in the setting of gatekeeper resistance (Table 1), including fusions, mutations, and acquired resistance mutations without evidence of FGFR1-mediated hyperphosphatemia (Fig 1B)

Table 1. LOXO-435 is potent and highly selective for FGFR3 and FGFR3 V555M enzymes while sparing FGFR1 and FGFR2

<table>
<thead>
<tr>
<th>Enzyme Inhibition</th>
<th>Fold Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1 IC50 (nM)</td>
<td>FGFR2 IC50 (nM)</td>
</tr>
<tr>
<td>FGFR3 IC50 (nM)</td>
<td>FGFR3 V555M IC50 (nM)</td>
</tr>
<tr>
<td>FGFR1 over FGFR3</td>
<td>FGFR1 over FGFR2</td>
</tr>
<tr>
<td>Endastinib</td>
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</tr>
<tr>
<td>Pemigatinib</td>
<td>0.5</td>
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<tr>
<td>Infragatib</td>
<td>0.4</td>
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<tr>
<td>Futibatinib</td>
<td>0.7</td>
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<tr>
<td>LOXO-435</td>
<td>108.2</td>
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</tbody>
</table>

Fig 1A. Tumor growth inhibition and regression with LOXO-435

Fig 1B. LOXO-435 does not increase serum phosphate

Study Design

This is a first-in-human, open-label, multicenter phase 1 study of LOXO-435 (NCT05614739)

Dose Escalation Phase 1a

(n=50-60) Cohort A All Solid Tumors

LOXO-435 monotherapy in patients with FGFR3-altered advanced solid tumors

- Single patient accelerated design

- mTPI-2 dose escalation with backfilling

- *Alteration in FGFR3 or ligand deemed clinically actionable (mutation, fusion, overexpression, or amplification) by the treating investigator
- mTPI-2, modified toxicity probability interval 2

Dose Expansion Phase 1b

(n=20 each) Cohort B: Metastatic Urothelial Carcinoma (UC) with activating FGFR3 alterations

B1: LOXO-435 monotherapy 
Prior FGFR inhibitor treatment required

B2: LOXO-435 monotherapy 
FGFR inhibitor naïve

B3: LOXO-435 + pembrolizumab 
FGFR inhibitor naïve

Cohort C: All non-UC Solid Tumors with activating FGFR3 alterations

C1: LOXO-435 monotherapy 
FGFR inhibitor naïve

- *Prespecified activating alterations

Study Objectives/Endpoints

Primary Objective

Secondary Objectives

Phase 1a

- Safety and tolerability
- PK properties of LOXO-435
- Investigator assessed ORR, DOR, TTR, PFS, DCR
- Overall survival

Phase 1b

- Investigator assessed ORR per RECIST v1.1.1

- Safety and tolerability
- Investigator assessed DOR, TTR, PFS, DCR
- Patient-reported symptomatic and functional responses (FACT-B1, FACT-PWB subscales)
- Overall survival

Abbreviations: DCR, disease control rate; DOR, duration of response; FACT-B1, Functional Assessment of Cancer Therapy-Bowel; FACT-PWB, Functional Assessment of Cancer Therapy-Physical Well-being; RECIST, response Evaluation Criteria in Solid Tumors; TTR, time to response

Eligibility Criteria

• Adults (≥18 years) with ECOG PS 0 or 1
• Measurable (required for phase 1b) or non-measurable disease per RECIST v1.1
• Locally advanced or metastatic solid tumor with an FGFR3 alteration detected by molecular testing in tumor or cDNA that is deemed to be clinically actionable
• Patients must have received all standard of care (SoC) therapy or must have refused the remaining most appropriate SoC therapy; or there is no SoC therapy available for the disease
• No restriction on number of prior therapies
• No primary CNS malignancy or uncontrolled CNS metastases
• No current evidence of corneal keratopathy or serious retinal disorder
• No significant cardiovascular disease, uncontrolled systemic infection, or extensive tissue calcification

Planned Study Sites

ACR Annual Meeting; Orlando, Florida; April 14–19, 2023
Presenter: Gopa Iyer (iyerg@mskcc.org)
Sponsored by Loxo Oncology at Lilly

References


Acknowledgments: Medical writing assistance was provided by Namal Bolaji, PhD, a full-time employee of Loxo/LLY
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Background

- Alterations in the fibroblast growth factor receptor 3 (FGFR3) have been identified as oncogenic drivers in solid tumor malignancies, including urothelial carcinoma
- Available pan-FGFR inhibitors target all 4 isoforms of FGFR (FGFR1-4) and consequently their efficacy can be limited by off-target toxicity including gastrointestinal, oral mucositis, and cutaneous/nail, as well as FGFR1-mediated hyperphosphatemia
- LOXO-435 is a potent, highly isoform-selective FGFR3 inhibitor that is designed to preserve activity in the setting of gatekeeper resistance mutations (Table 1)
- In preclinical studies, LOXO-435 demonstrated potent and selective activity in both wild-type and oncogenically activated FGFR3 (Fig 1A), including fusions, mutations, and acquired resistance mutations without evidence of FGFR1-mediated hyperphosphatemia (Fig 1B)
Table 1. LOXO-435 is potent against and highly selective for FGFR3 and FGFR3 V555M enzymes while sparing FGFR1 and FGFR2³

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**Figure 1A. Tumor growth inhibition and regression with LOXO-435**

**Figure 1B. LOXO-435 does not increase serum phosphate**

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**Background**

- This phase 1 study is investigating safety and efficacy of LOXO-435 as monotherapy and with pembrolizumab in patients with FGFR3-altered tumors.
This is a first-in-human, open-label, multicenter phase 1 study of LOXO-435 (NCT05614739)

**Study Design**

**Dose Escalation Phase 1a**

- Cohort A: All Solid Tumors
  - LOXO-435 monotherapy in patients with FGFR3-altered advanced solid tumors
  - Single patient accelerated design
  - mTPI-2 dose escalation with backfilling

**Dose Expansion Phase 1b**

- Cohort B: Metastatic Urothelial Carcinoma (UC) with activating FGFR3 alterations
  - B1: LOXO-435 monotherapy
    - Prior FGFR inhibitor treatment required
  - B2: LOXO-435 monotherapy
    - FGFR inhibitor naive
  - B3: LOXO-435 + pembrolizumab
    - FGFR inhibitor naive

- Cohort C: All non-UC Solid Tumors with activating FGFR3 alterations
  - C1: LOXO-435 monotherapy
    - FGFR inhibitor naive

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*a* Alteration in FGFR3 or its ligands deemed clinically actionable (mutation, fusion, overexpression, or amplification) by the treating investigator

mTPI-2, modified toxicity probability interval-2

*b* Prespecified activating alterations
### Study Objectives/Endpoints

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<th>Phase 1a</th>
<th>Primary Objective</th>
<th>Secondary Objectives</th>
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|          | RP2D of LOXO-435  | Safety and tolerability  
|          |                   | PK properties of LOXO-435  
|          |                   | Investigator assessed ORR, DOR, TTR, PFS, DCR  
|          |                   | Overall survival  |

<table>
<thead>
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<th>Phase 1b</th>
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<th>Secondary Objectives</th>
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|          | Investigator assessed ORR per RECIST v1.1. | Safety and tolerability  
|          |                   | Investigator assessed DOR, TTR, PFS, DCR  
|          |                   | Patient-reported symptomatic and functional responses (FACT-BI, FACT-PWB subscales)  
|          |                   | Overall survival  |

**Abbreviations:** DCR, disease control rate; DOR, duration of response; FACT-B1, Functional Assessment of Cancer Therapy-Bladder; FACT-PWB, Functional Assessment of Cancer Therapy-Physical Well-being; RECIST, response Evaluation Criteria in Solid Tumors; TTR, time to response
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• No restriction on number of prior therapies
• No primary CNS malignancy or uncontrolled CNS metastases
• No current evidence of corneal keratopathy or serious retinal disorder
• No significant cardiovascular disease, uncontrolled systemic infection, or extensive tissue calcification
Planned Study Sites

- Canada
- United States of America
- France
- Germany
- Italy
- Netherlands
- Norway
- Spain
- United Kingdom
- China
- Japan
- South Korea
- Australia
- Israel
References
4. Unpublished. Data on file at Loxo@Lilly

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